Bram Rochwerg, MD, MSc (Epi), FRCPC, Series Editor

Induction Agents for Tracheal Intubation in Critically Ill Patients

Yuki Kotani, MD[1]
Vincenzo Russotto, MD[2,3]

OBJECTIVES: Concise definitive review of the use of induction agents in critically ill patients undergoing tracheal intubation and their association with outcomes.

DATA SOURCES: Original publications were retrieved through a PubMed search with search terms related to induction agents for tracheal intubation in critically ill patients.

STUDY SELECTION: We included randomized controlled trials and observational studies that reported patient outcomes.

DATA EXTRACTION: Data from included studies, including choice of induction agents and clinically relevant outcomes, were extracted.

DATA SYNTHESIS: Etomidate and ketamine have been the most studied induction agents in critical care during last years. Recent studies on etomidate investigated the clinical impact of its recognized adrenal suppression in terms of morbidity and mortality. Etomidate may carry a non-negligible mortality risk without definitive hemodynamic benefits compared with ketamine. Available data then support the use of ketamine over etomidate, since the difference in the hemodynamic profile seems to be of minor clinical relevance. No multicenter randomized studies are available comparing propofol to other induction agents but evidence from a large observational study identified an association of propofol with post-intubation cardiovascular instability in critically ill patients. Despite the observational nature of these findings cannot exclude the role of confounders, the association of propofol with post-induction cardiovascular instability is pharmacologically plausible, justifying its avoidance in favor of drugs with a better safety profile in critical care such as ketamine.

CONCLUSIONS: Although no definitive conclusions can be drawn based on the available evidence, recent evidence pointed out the potential negative effect of etomidate on survival and the association of propofol with cardiovascular instability. Ketamine may be considered the drug with a safer profile, widespread availability and low cost but future research should provide definitive data on optimal drug selection, its dosage in the context of critical illness and concomitant interventions to minimize the risk of peri-intubation complications.

KEYWORDS: etomidate; intensive care units; intubation; ketamine; mortality; propofol

Tracheal intubation is one of the most performed procedures in the critically ill with a high risk of complications related to the already existing considerable physiological derangements, including hypoxemia, hypotension, and metabolic acidosis (1). In the International Observational Study to Understand the Impact and Best Practices of Airway Management in Critically Ill Patients (INTUBE) study, up to 45% of patients suffered from major peri-intubation adverse events and peri-intubation cardiovascular instability was the most common event, registered in up to 43% of patients, followed by hypoxemia in 9%, and post-intubation cardiac arrest in 3% of patients (2). Furthermore,

Copyright © 2024 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

DOI: 10.1097/CCM.0000000000006506

Copyright © 2024 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

SHOUT
SHARE
IT

critically ill patients experiencing post-induction hypotension (registered up to 30 min after induction) may be associated with a higher ICU (adjusted odds ratio [OR], 2.47; 95% CI, 1.72–3.55) and 28-day mortality (adjusted OR, 2.52; 95% CI, 1.72–3.68), compared with patients not experiencing peri-intubation adverse events (3). To minimize such adverse events, research during the last years focused on strategies to achieve first-pass intubation success and optimize peri-intubation physiology in the attempt to limit the derangements associated with induction, apnea and transition from negative to positive pressure ventilation (4–8).

Induction drugs are a fundamental component of rapid sequence intubation/induction bundle. They provide amnesia, blunt sympathetic response and, along with muscle relaxants, contribute to improve intubating conditions (9). Different induction agents have peculiarities and clinicians may select them based on their specific properties, for example, ketamine in severe asthma, given the bronchodilatory effect of this drug. However, the large majority of research on induction agents in critical care focused on their different impact on patient's hemodynamics, as the administration of induction agents is frequently accompanied by hypotension due to diminished sympathetic nervous tone. For instance, ketamine and etomidate have similar hemodynamic tolerance, while propofol is an independent risk factor of peri-intubation cardiovascular instability. Although many confounders may play a role, these data underscore the need for the optimal induction agent selection with minimal hemodynamic compromise to prevent peri-intubation adverse events, particularly hypotension, and improve clinical outcomes in critically ill patients with reduced physiology reserve (**Fig. 1**). This concise definitive review aims to overview the current understanding of how to choose the optimal induction agent in the context of critical illness.

PHARMACOLOGIC PROPERTIES AND CLINICAL IMPLICATIONS OF INDUCTION AGENTS

Propofol

Propofol is a lipid-soluble alkylphenol derivative that binds to the gamma-aminobutyric acid (GABA) receptor causing sedation and amnesia. It is the most used induction drug in anesthesia, given its rapid onset and reproducible pharmacokinetic properties. Additional

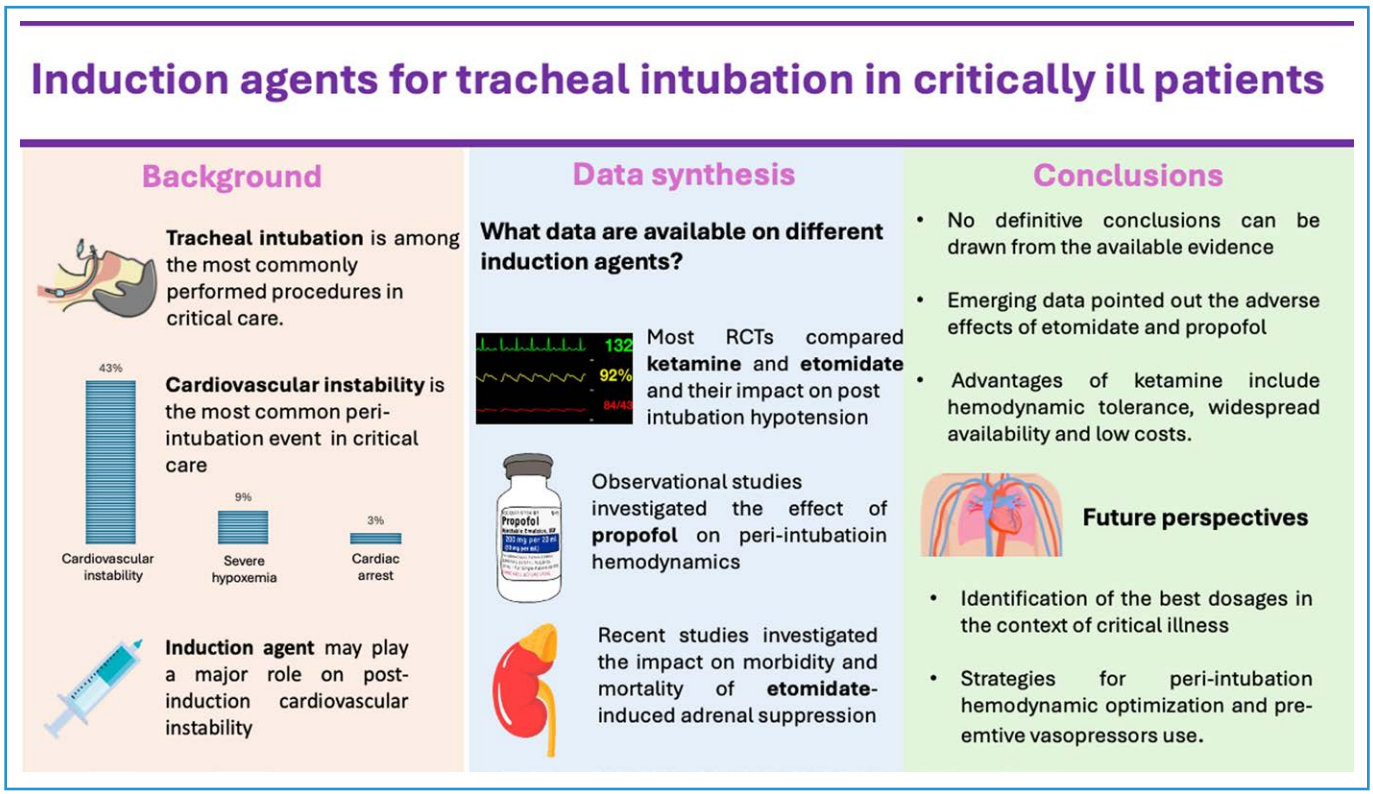
Induction agents for tracheal intubation in critically ill patients
Background
Tracheal intubation is among the most commonly performed procedures in critical care.
43%
9%
3%
Cardiovascular instability
Severe hypoxemia
Cardiac arrest
Cardiovascular instability is the most common peri-intubation event in critical care
Induction agent may play a major role on post-induction cardiovascular instability
Data synthesis
What data are available on different induction agents?
132
92%
84/43
Most RCTs compared ketamine and etomidate and their impact on post intubation hypotension
Propofol
Observational studies investigated the effect of propofol on peri-intubatioin hemodynamics
Recent studies investigated the impact on morbidity and mortality of etomidate-induced adrenal suppression
Conclusions
No definitive conclusions can be drawn from the available evidence
Emerging data pointed out the adverse effects of etomidate and propofol
Advantages of ketamine include hemodynamic tolerance, widespread availability and low costs.
Future perspectives
Identification of the best dosages in the context of critical illness
Strategies for peri-intubation hemodynamic optimization and pre-emtive vasopressors use.

Figure 1. Induction agents for tracheal intubation in critically ill patients: evidence summary. RCTs = randomized controlled trials.

Copyright © 2024 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

useful features are the reduction of airway resistance and its neuroinhibitory effects (10). Negative properties arise from the suppression of sympathetic activity and its associated myocardial depression and peripheral vasodilation (11, 12), potentially leading to poor clinical outcomes (13). Of importance, higher doses of propofol on induction are associated with a more profound decrease of both systolic and diastolic blood pressures and with a higher frequency of apnea, especially in older patients (14). These effects may have a major impact in critically ill patients presenting with a different degree of cardiac function impairment and hypovolemia (**Table 1**).

Midazolam

Midazolam is a short acting benzodiazepine with sedative and amnesic properties resulting from GABA receptor complex agonism. Like all benzodiazepines, midazolam has not analgesic properties. Its antiseizure effect makes it an option for induction of patients with status epilepticus (15). At the routine induction dose of 0.2 mg/kg, it has been associated with a reduction of mean arterial pressure in healthy patients up to 25%. This hemodynamic effect may become more pronounced and clinically relevant in critically ill patients with hypovolemia and shock and with a dose-response relationship (16). The reduction of induction dose in the attempt to limit the hemodynamic impact of midazolam can be associated with a clinically relevant delay of onset of intubation conditions and of the deep of sedation achieved (17). Furthermore, sedation with benzodiazepine increases the risk of delirium (18). Given all these limitations, midazolam is rarely used as the single induction drug, while it is more frequently added in small doses (1–2 mg in a normal weight adult patient) to the main induction drug (e.g., ketamine) to benefit from its amnesic properties.

Etomidate

Etomidate binds to the GABA type A receptor, specifically at the beta subunit, in the CNS, thereby increasing the affinity of the receptor for GABA. This enhanced affinity leads to hyperpolarization of the neurons, which reduces excitability of neurons and induces hypnosis. Due to its rapid onset and minimal effects on cardiovascular stability, etomidate is frequently used as an induction agent for tracheal intubation in critically ill patients (2), although its availability is limited in some countries. The major concern of etomidate is the development of adrenal insufficiency. Etomidate suppresses the production of cortisol through inhibiting 11-beta-hydroxylase, a key enzyme for cortisol and aldosterone synthesis (19). Adrenal suppression typically lasts from several hours to days (19). Given that etomidate is preferably administered in hemodynamically unstable patients, adrenal suppression may further complicate circulatory management.

Ketamine

Among various hypnotic agents, ketamine has a unique mechanism of action that involves glutamate, an excitatory neurotransmitter. By acting as a noncompetitive antagonist of N-methyl-D-aspartate receptors, ketamine blocks excitatory neurotransmission pathway triggered by glutamate and induces a dissociate anesthesia. Induction with ketamine carries several beneficial properties for tracheal intubation in the critical care setting. For example, by inhibiting presynaptic catecholamine reuptake and increasing norepinephrine levels at postsynaptic receptors, ketamine stimulates the sympathetic nervous system, leading to an increase in heart rate, blood pressure, and cardiac output (20). All these effects can contribute to preventing peri-intubation cardiovascular collapse, especially in hemodynamically unstable patients. It remains uncertain if ketamine is better than etomidate in terms of restoring hemodynamic stability. Unlike other hypnotic agents, ketamine has minor effects on respiratory function. As such, maintained spontaneous breathing and preserved airway reflex are also key features, which are helpful in patients with severe hypoxemia or at high risk of aspiration. In addition, ketamine has bronchodilation effect, which is protective for obstructive lung diseases like asthma attack. Adverse events of ketamine are hallucinations, nightmare, and hypersalivation (21–23). Unfortunately, assessment of these symptoms has been rarely conducted in critically ill settings and their clinical significance remains uncertain. Ketamine was traditionally concerned for increasing intracranial pressure (24); however, recent literature suggest that intracranial pressure is not affected or even reduced with ketamine administration in patients with acute brain injury (25–27). Therefore, there is no convincing evidence to support the association between ketamine use and increased intracranial

Copyright © 2024 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

TABLE 1.
Characteristics of Induction Agents

Induction Agent	Binding Receptor	Dose	Hemodynamic Effects	Respiratory Effects	Special Considerations
Propofol	GABA receptor	1–3 mg/kg	Reduced myocardial contractility Vasodilation	Bronchodilation Suppression of upper airway reflexes	Anti-epileptic effects No analgesic effect
Etomidate	GABA receptor	0.3 mg/kg	Hemodynamic stability Adrenal insufficiency	Smaller impact on respiratory system compared with propofol and barbiturates	No analgesic effect Myoclonus
Ketamine	N-methyl-D-aspartate receptor	1–2 mg/kg	Hemodynamic stability	Bronchodilation Spontaneous breathing preservation	Analgesic effect Hallucinations Nightmares Hypersalivation
Midazolam	GABA receptor	0.1–0.3 mg/kg	Hypotension	Respiratory drive depression, especially in older patients	Anti-epileptic effects
Fentanyl	Opioid receptor	1–3 μg/kg	Hypotension	Chest wall rigidity Fentanyl-induced cough Respiratory drive depression	Enhanced respiratory and hemodynamic effects in coadministration with hypnotics
Thiopental	GABA receptor	3–5 mg/kg	Venodilation Negative inotropic effects	Bronchospasm	Neuronal activity suppression

GABA = gamma-aminobutyric acid.

Copyright © 2024 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

pressure, while avoiding peri-intubation hypotension is of pivotal importance to maintain an adequate cerebral perfusion pressure in this circumstance (28). In addition to the above-mentioned pharmacological characteristics, ketamine is inexpensive and easily available, making it a useful induction agent also in resource-limited settings.

Thiopental

Barbiturates are no longer readily available and, given a number of potential detrimental effects, are rarely used in the setting of induction of a critically ill patient. Thiopental is one of the ultra-short-acting barbiturates that act on the barbiturate component of the GABA receptor complex to induce sedation. It exerts venous dilation and negative inotropic effects, resulting in hypotension in the doses used for induction (29). Furthermore, thiopental leads to histamine release inducing bronchospasm and, therefore, should be avoided in patients with reactive airway disease (30). Both in vitro and in vivo evidence reported a suppression of blood cell recruitment, activation and activity triggered by thiopental, raising concern on its use in septic patients (31). To summarize, there is no indication for the use of thiopental in place of other more commonly used agents.

Combination of Induction Drugs

In addition to the induction agent described above, some other drugs may be used in combination during induction of critically ill patients. Fentanyl may be co-administered with hypnotic agents, with the aim to blunt the sympathetic response triggered by pain associated with airway instrumentation or with underlying disease (32). A randomized trial compared fentanyl with placebo in addition to ketamine and rocuronium among patients undergoing emergency intubation (33). Fentanyl increased the risk of hypotension (29% vs. 16%; risk difference, 13%; 95% CI, 3–23) but did not affect other relevant outcomes including first-pass success rate or mortality (33), which supports its avoidance to maintain hemodynamic stability.

An admixture of ketamine and propofol (ketofol) may offset the hemodynamic instability driven by propofol through the sympathetic stimulation of ketamine. A randomized trial comparing ketofol with etomidate in 163 patients undergoing emergent intubation found no difference in post-induction hemodynamic conditions, suggesting its favorable hemodynamic profile (34). However, the admixture ratio is neither well-defined, standardized, nor approved (34–36).

EMERGING CLINICAL EVIDENCE AND GUIDELINES RECOMMENDATIONS

During last years, evidence on hypnotic drug selection and clinical outcomes has accumulated, mainly focusing on two induction drugs—ketamine and etomidate—having the most favorable hemodynamic profile for the critically ill. Guidelines on tracheal intubation of the critically ill patient by the Difficult Airway Society (37) supported the use of ketamine as the elective choice in critical care, after considering concerns on etomidate-induced adrenal suppression (38, 39), while several national guidelines recommend the use of ketamine or etomidate as induction agents for tracheal intubation in the ICU (40, 41). More recently, the Society of Critical Care Medicine (SCCM) has published practice guidelines for rapid sequence intubation in critically ill adult patients (42). From the analyzed evidence, the SCCM guidelines did not detect any meaningful difference of etomidate compared with ketamine so that, given its availability, experience with its use and low cost, etomidate is considered a reasonable option for rapid sequence induction in critical care (42). However, emerging evidence has added new insights to these relatively neutral guideline statements. A recent randomized trial by Matchett et al (43) comparing etomidate with ketamine in 801 critically ill patients found an increased 7-day mortality in the etomidate group (23% vs. 15%; difference, 7.8%; 95% CI, 2.4–13). A subsequent meta-analysis by Kotani et al (44) showed that etomidate, compared with any other induction agent (not limited to ketamine), was associated with an increased risk of mortality (risk ratio, 1.16; 95% CI, 1.01–1.33). The Bayesian analysis, applied in this meta-analysis, confirmed that a probability of mortality increase was as high as 98.1% (44). Of note, in this meta-analysis, comparators of etomidate were midazolam in four randomized controlled trials (RCTs), ketamine in four RCTs, ketamine plus midazolam in one RCT, ketamine plus propofol in one RCT, and thiopental in one RCT (44). Although the short-term mortality difference was not translated in long-term in the largest but single-center randomized trial (28-d mortality, 36% vs. 33%; difference, 2.7%;

Copyright © 2024 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

95% CI, –3.9 to 9.3) (43) or in meta-analysis (mortality at the longest follow-up, 27% vs. 25%; risk ratio, 1.07; 95% CI, 0.95–1.21) (44), it is important to recognize the potential mortality harm of etomidate. Concerning the hemodynamic effects, in the RCT by Matchett et al (43), ketamine increased the rate of post-induction cardiovascular collapse and the need of rescue vasopressors, while no difference in post-induction mean arterial pressure or drop of systolic blood pressure after induction was observed between the ketamine and etomidate groups. Taken as a whole, etomidate may carry a non-negligible mortality risk without definitive hemodynamic benefits compared with ketamine. Available data then support the use of ketamine over etomidate, since the difference in the hemodynamic profile, if present, seems to be of not clinical relevance and could be balanced by preemptive or rescue vasopressors, while etomidate seems to expose patient to a higher mortality risk (43).

Propofol is widely used as an induction agent in the operating room but has some concerning effects on hemodynamics (36, 39, 40), which prompted evaluation in critically ill settings. Several guidelines pointed out the higher risk of cardiovascular collapse driven by propofol (37, 40, 41), while the SCCM guidelines suggested no difference between propofol and etomidate in terms of mortality or the frequency of hypotension or vasopressor use during the peri-intubation period (42). A secondary analysis of INTUBE study investigated variables associated with post-intubation cardiovascular instability (3). After applying the inverse probability of treatment weighting method to balance the population for covariates potentially associated with post-intubation cardiovascular instability, propofol was identified as the unique modifiable intervention associated with a higher frequency of post-induction cardiovascular instability, irrespective of the baseline blood pressure (adjusted OR, 1.23; 95% CI, 1.02–1.49) (3). Propofol was used in 41.4% worldwide, either as the single hypnotic agent or in combination with other molecules (e.g., ketamine, etomidate) (3). The median overall dose of propofol was 1.12 mg/kg (interquartile range, 0.71–1.67 mg/kg) (3). Interestingly, propofol was significantly more commonly used by anesthesiologists, who administered it in 49% of patients, compared with nonanesthesiologists (intensivists and emergency physicians), who administered it in 32% of patients (3). Of note, the association of propofol with a worse hemodynamic outcome was detected also when added in a mix of other induction molecules (3). Although complex drug-drug interactions may be of importance, the profound influence of propofol on hemodynamic status, especially at the high administration rate used during rapid sequence induction, may play an important role also at the low doses typically used in co-induction with other molecules (43, 44). Despite the observational nature of these findings cannot exclude the role of confounders, the adverse associations are pharmacologically plausible, justifying the avoidance of propofol to reduce the risk of hemodynamic collapse in favor of drugs with a better safety profile in critical care such as ketamine (45).

FUTURE PERSPECTIVES

Despite intense investigation conducted recently, several key questions have yet to be answered. First, an important question is which type of induction agent can most effectively avoid peri-intubation cardiovascular instability. Given their hemodynamically tolerant profile, the most studied comparison was one between ketamine and etomidate (44, 46). However, prior randomized trials have important limitations including single-center design, inadequate sample size, and a lack of long-term follow-up. An ongoing RCT (NCT05277896) will overcome the main limitations of previous trials, thanks to the large sample size, multicenter design and long-term outcome follow-up (NCT06179485), and thus will add robust data to the body of evidence (47, 48). Another unmet need is identification of optimal dosing strategies. Hypnotic agents exert their effects in a dose-dependent manner. In critical settings, it is crucial to achieve an adequate level of sedation while minimizing the risk of adverse events. However, there is currently no reliable prediction model to determine the hypnotic dosage while ensuring the effectiveness and safety at the same time.

Second, in parallel to the optimal induction agent selection and dosing, preemptive vasopressor use is a promising strategy to reduce post-induction hypotension. Indeed, a preemptive increase of vasomotor tone may counterbalance the negative hemodynamic effects of induction, which have been registered also in patients with adequate baseline hemodynamics (47). An ongoing multicenter RCT (NCT05014581) will address this relevant question with the hypothesis that

Copyright © 2024 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

TABLE 2.
Current Knowledge Gaps and Future Research Priorities

Knowledge Gaps	Future Studies
Optimal type of induction agent to avoid cardiovascular instability	A large-scale multicenter randomized controlled trial comparing ketamine and etomidate to evaluate their effects on peri-intubation cardiovascular instability and long-term patient outcomes
Optimal dosage of induction agent	Dose-response relationship of each induction agent in terms of hemodynamic stability Development of clinical prediction models to considering induction dosage and patient clinical status (e.g., preintubation hemodynamic parameters)
Preemptive use of vasopressors to mitigate post-induction cardiovascular collapse	An international multicenter randomized controlled trial on preemptive infusion of noradrenaline is ongoing (Preventing caRdiovascular collapsE with VasoprEssors duriNg Tracheal IntubatiON [PREVENTION] trial, NCT05014581)
Efficacy and safety of remimazolam as an induction agent in critically ill patients	Prospective studies comparing remimazolam with ketamine or etomidate to assess the applicability of remimazolam in critically ill settings

preemptive noradrenaline administration would mitigate the frequency and severity of peri-intubation cardiovascular collapse (49).

Finally, an emerging benzodiazepine, remimazolam, has provided some promising results. Due to its hemodynamic tolerant property, remimazolam resulted in less frequent hypotension and bradycardia than propofol for sedation during endoscopic procedures in noncritically ill settings (50). Such hemodynamic stability was also confirmed when remimazolam was used for induction and maintenance of general anesthesia in patients undergoing cardiac procedures (51). These findings warrant prospective evaluation of its efficacy and safety as an induction agent in the critically ill population.

The knowledge gaps and future perspectives are summarized in **Table 2** and Figure 1.

CONCLUSIONS

Despite the lack of solid evidence showing superiority of one agent to others, the best available evidence suggests that induction with propofol or etomidate appears to be associated with adverse clinical outcomes. Major advantages of ketamine include hemodynamic tolerance, widespread availability and low cost. Regardless of the chosen agent, it is crucial to implement preventive measures to minimize the risk of adverse peri-intubation events, which occur frequently and are associated with increased mortality. Future investigation is warranted to determine the optimal type and dose of induction agent considering patient heterogeneity and concomitant interventions.

1 *Department of Intensive Care Medicine, Kameda Medical Center, Kamogawa, Japan.*

2 *Department of Anesthesia and Critical Care, AOU S. Luigi Gonzaga, Orbassano, Turin, Italy.*

3 *Department of Oncology, University of Turin, Turin, Italy.*

The authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: vincenzo.russotto@unito.it

REFERENCES

1. De Jong A, Myatra SN, Roca O, et al: How to improve intubation in the intensive care unit. Update on knowledge and devices. *Intensive Care Med* 2022; 48:1287–1298
2. Russotto V, Myatra SN, Laffey JG, et al; INTUBE Study Investigators: Intubation practices and adverse peri-intubation events in critically ill patients from 29 countries. *JAMA* 2021; 325:1164–1172
3. Russotto V, Tassistro E, Myatra SN, et al: Peri-intubation cardiovascular collapse in patients who are critically ill: Insights from the INTUBE study. *Am J Respir Crit Care Med* 2022; 206:449–458
4. Janz DR, Casey JD, Semler MW, et al; PrePARE Investigators: Effect of a fluid bolus on cardiovascular collapse among critically ill adults undergoing tracheal intubation (PrePARE): A randomised controlled trial. *Lancet Respir Med* 2019; 7:1039–1047
5. Russell DW, Casey JD, Gibbs KW, et al; PREPARE II Investigators and the Pragmatic Critical Care Research Group: Effect of fluid bolus administration on cardiovascular collapse

Copyright © 2024 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

among critically ill patients undergoing tracheal intubation: A randomized clinical trial. *JAMA* 2022; 328:270–279

6. Frat J-P, Ricard J-D, Quenot J-P, et al; FLORALI-2 study group: Non-invasive ventilation versus high-flow nasal cannula oxygen therapy with apnoeic oxygenation for preoxygenation before intubation of patients with acute hypoxaemic respiratory failure: A randomised, multicentre, open-label trial. *Lancet Respir Med* 2019; 7:303–312
7. Prekker ME, Driver BE, Trent SA, et al: Video versus direct laryngoscopy for tracheal intubation of critically ill adults. *N Engl J Med* 2023; 389:418–429
8. Gibbs KW, Semler MW, Driver BE, et al; PREOXI Investigators and the Pragmatic Critical Care Research Group: Noninvasive ventilation for preoxygenation during emergency intubation. *N Engl J Med* 2024; 390:2165–2177
9. Russotto V, Rahmani LS, Parotto M, et al: Tracheal intubation in the critically ill patient. *Eur J Anaesthesiol* 2022; 39:463–472
10. Sahinovic MM, Struys MMRF, Absalom AR: Clinical pharmacokinetics and pharmacodynamics of propofol. *Clin Pharmacokinet* 2018; 57:1539–1558
11. Dietrich SK, Mixon MA, Rogoszewski RJ, et al: Hemodynamic effects of propofol for induction of rapid sequence intubation in traumatically injured patients. *Am Surg* 2018; 84:1504–1508
12. Kotani Y, Pruna A, Landoni G: Mechanisms of action of the detrimental effects of propofol on survival. *J Cardiothorac Vasc Anesth* 2023; 37:2176–2180
13. Kotani Y, Pruna A, Turi S, et al: Propofol and survival: An updated meta-analysis of randomized clinical trials. *Crit Care* 2023; 27:139
14. Peacock JE, Lewis RP, Reilly CS, et al: Effect of different rates of infusion of propofol for induction of anaesthesia in elderly patients. *Br J Anaesth* 1990; 65:346–352
15. Peter J-U, Dieudonné P, Zolk O: Pharmacokinetics, pharmacodynamics, and side effects of midazolam: A review and case example. *Pharmaceuticals* 2024; 17:473
16. Davis DP, Kimbro TA, Vilke GM: The use of midazolam for prehospital rapid-sequence intubation may be associated with a dose-related increase in hypotension. *Prehosp Emerg Care* 2001; 5:163–168
17. Sagarin MJ, Barton ED, Sakles JC, et al; National Emergency Airway Registry Investigators: Underdosing of midazolam in emergency endotracheal intubation. *Acad Emerg Med* 2003; 10:329–338
18. Devlin JW, Skrobik Y, Gélinas C, et al: Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med* 2018; 46:e825–e873
19. Dalia AA, Raines DE: Etomidate and adrenocortical suppression: Should we take the concerns to heart? *J Cardiothorac Vasc Anesth* 2021; 35:1086–1088
20. Hurth KP, Jaworski A, Thomas KB, et al: The reemergence of ketamine for treatment in critically ill adults. *Crit Care Med* 2020; 48:899–911
21. Blagrove M, Morgan CJA, Curran HV, et al: The incidence of unpleasant dreams after sub-anaesthetic ketamine. *Psychopharmacology (Berl)* 2009; 203:109–120
22. Trimmel H, Helbok R, Staudinger T, et al: S(+)-ketamine: Current trends in emergency and intensive care medicine. *Wien Klin Wochenschr* 2018; 130:356–366
23. Zanos P, Moaddel R, Morris PJ, et al: Ketamine and ketamine metabolite pharmacology: Insights into therapeutic mechanisms. *Pharmacol Rev* 2018; 70:621–660
24. Green SM, Andolfatto G, Krauss BS: Ketamine and intracranial pressure: No contraindication except hydrocephalus. *Ann Emerg Med* 2015; 65:52–54
25. Gregers MCT, Mikkelsen S, Lindvig KP, et al: Ketamine as an anesthetic for patients with acute brain injury: A systematic review. *Neurocrit Care* 2020; 33:273–282
26. Godoy DA, Badenes R, Pelosi P, et al: Ketamine in acute phase of severe traumatic brain injury "an old drug for new uses?". *Crit Care* 2021; 25:1–7
27. Laws JC, Vance EH, Betters KA, et al: Acute effects of ketamine on intracranial pressure in children with severe traumatic brain injury. *Crit Care Med* 2023; 51:563–572
28. Ziai WC, Thompson CB, Mayo S, et al; Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage (CLEAR III) Investigators: Intracranial hypertension and cerebral perfusion pressure insults in adult hypertensive intraventricular hemorrhage: Occurrence and associations with outcome. *Crit Care Med* 2019; 47:1125–1134
29. Russo H, Bressolle F: Pharmacodynamics and pharmacokinetics of thiopental. *Clin Pharmacokinet* 1998; 35:95–134
30. Hirota K, Ohtomo N, Hashimoto Y, et al: Effects of thiopental on airway calibre in dogs: Direct visualization method using a superfine fibreoptic bronchoscope. *Br J Anaesth* 1998; 81:203–207
31. Ploppa A, Kiefer R-T, Nohé B, et al: Dose-dependent influence of barbiturates but not of propofol on human leukocyte phagocytosis of viable *Staphylococcus aureus*. *Crit Care Med* 2006; 34:478–483
32. Ferguson I, Bliss J, Aneman A: Does the addition of fentanyl to ketamine improve haemodynamics, intubating conditions or mortality in emergency department intubation: A systematic review. *Acta Anaesthesiol Scand* 2019; 63:587–593
33. Ferguson I, Buttfield A, Burns B, et al; Australasian College for Emergency Medicine Clinical Trials Network: Fentanyl versus placebo with ketamine and rocuronium for patients undergoing rapid sequence intubation in the emergency department: The FAKT study—A randomized clinical trial. *Acad Emerg Med* 2022; 29:719–728
34. Smischney NJ, Nicholson WT, Brown DR, et al: Ketamine/propofol admixture vs etomidate for intubation in the critically ill: KEEP PACE randomized clinical trial. *J Trauma Acute Care Surg* 2019; 87:883–891
35. Hui TW, Short TG, Hong W, et al: Additive interactions between propofol and ketamine when used for anesthesia induction in female patients. *Anesthesiology* 1995; 82:641–648
36. Smischney NJ, Beach ML, Loftus RW, et al: Ketamine/propofol admixture (ketofol) is associated with improved hemodynamics as an induction agent: A randomized, controlled trial. *J Trauma Acute Care Surg* 2012; 73:94–101
37. Higgs A, McGrath BA, Goddard C, et al; Difficult Airway Society: Guidelines for the management of tracheal intubation in critically ill adults. *Br J Anaesth* 2018; 120:323–352
38. Albert SG, Ariyan S, Rather A: The effect of etomidate on adrenal function in critical illness: A systematic review. *Intensive Care Med* 2011; 37:901–910

Copyright © 2024 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.

39. Bruder EA, Ball IM, Ridi S, et al: Single induction dose of etomidate versus other induction agents for endotracheal intubation in critically ill patients. *Cochrane Database Syst Rev* 2015; 1:CD010225
40. Myatra SN, Ahmed SM, Kundra P, et al: Republication: All India difficult airway association 2016 guidelines for tracheal intubation in the intensive care unit. *Indian J Crit Care Med* 2017; 21:146–153
41. Quintard H, l'Her E, Pottecher J, et al: Experts' guidelines of intubation and extubation of the ICU patient of French Society of Anaesthesia and Intensive Care Medicine (SFAR) and French-speaking Intensive Care Society (SRLF). *Ann Intensive Care* 2019; 9:13
42. Acquisto NM, Mosier JM, Bittner EA, et al: Society of Critical Care Medicine clinical practice guidelines for rapid sequence intubation in the critically ill adult patient. *Crit Care Med* 2023; 51:1411–1430
43. Matchett G, Gasanova I, Riccio CA, et al; EvK Clinical Trial Collaborators: Etomidate versus ketamine for emergency endotracheal intubation: A randomized clinical trial. *Intensive Care Med* 2022; 48:78–91
44. Kotani Y, Piersanti G, Maiucci G, et al: Etomidate as an induction agent for endotracheal intubation in critically ill patients: A meta-analysis of randomized trials. *J Crit Care* 2023; 77:154317
45. Karamchandani K, Nasa P, Jarzebowski M, et al: Tracheal intubation in critically ill adults with a physiologically difficult airway. An international Delphi study. *Intensive Care Med* 2024; 50:1563–1579
46. Koroki T, Kotani Y, Yaguchi T, et al: Ketamine versus etomidate as an induction agent for tracheal intubation in critically ill adults: A Bayesian meta-analysis. *Crit Care* 2024; 28:48
47. ClinicalTrials.gov: NCT05277896: Randomized Trial of Sedative Choice for Intubation (RSI). Available at: https://clinicaltrials.gov/ct2/show/NCT05277896. Accessed April 25, 2024
48. ClinicalTrials.gov: Effect of Ketamine and Etomidate During RSI on Long Term Outcomes (RSI-LTO). Available at: https://clinicaltrials.gov/study/NCT06179485. Accessed April 25, 2024
49. ClinicalTrials.gov: NCT05014581: Preventing Cardiovascular Collapse With Vasopressors During Tracheal Intubation (PREVENTION). Available at: https://classic.clinicaltrials.gov/ct2/show/NCT05014581. Accessed April 25, 2024
50. Barbosa EC, Espírito Santo PA, Baraldo S, et al: Remimazolam versus propofol for sedation in gastrointestinal endoscopic procedures: A systematic review and meta-analysis. *Br J Anaesth* 2024; 132:1219–1229
51. Ripoll JG, Orjuela RB, Kanaparthi A, et al: Remimazolam in cardiac anesthesia: Analysis of recent data. *J Cardiothorac Vasc Anesth* 2024 Aug 22. [online first]

Copyright © 2024 by the Society of Critical Care Medicine and Wolters Kluwer Health, Inc. All Rights Reserved.